Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 63, 68-76, 78-88, 94, 95 and 97-133 are pending in the application, with claim 63 being the sole independent claim. Claims 1-3, 15, 19, 21-34, 55, 64-67, 77, 89-93 and 96 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 74 has been withdrawn form consideration by the Examiner. New claims 97-133 are sought to be added. Support for the amendments can be found in paragraphs [0006], [0020], [0061] and [0063] of the published application, as well as in original claims 32, 33, 34, 55, 61 and 62. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 103

I. Claims 1-3, 15, 19, 21-34, 55, 63, 64, 76-85 and 91-95

The Examiner has maintained the rejection of claims 1-3, 15, 19, 21-31, 32-34, 55, 63, 64, 76-85 and 91-95 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel *et al.* (U.S. Patent No. 6,964 769 B2, hereinafter "Sebbel") view of Kojima *et al.* (Nature, 1999, hereinafter "Kojima"). The Examiner asserts that "Sebbel teaches VLPs and Q-beta phage conjugated antigens, which form repetitive arrays." Office Action at page 5. The Examiner also asserts that "Sebbel teaches a VLP bacteriophage

coupled to an antigen by way of non-peptide bond." Office Action at page 6. The Examiner further asserts that "because Sebbel teaches the claim limitation such an ordered and repetitive antigen array with VLP bacteriophage by way of non-peptide bond it would have been obvious to the skilled person in the art to provide the composition of the present invention." Office Action at page 6. Additionally, the Examiner asserts that Kojima "teach a human ghrelin peptide, which has the sequence of the instantly claimed SEQ ID NO: 31." Office Action at page 7. Applicants respectfully disagree with the Examiner's assertions and the conclusion based thereon. Claims 1-3, 15, 19, 21-34, 55, 64, 77 and 91-93 have been canceled. Insofar as the rejection may apply to the remaining presently pending claims, Applicants respectfully traverse this rejection.

The references cited by the Examiner do not disclose all of the elements of the present claims. Thus, the Examiner has not satisfied the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). The factors to be considered under 35 U.S.C. § 103(a) are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and MPEP §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 127 S.Ct. 1727 (2007). The critical role of the Office personnel as fact finders when resolving *Graham* inquiries has recently been emphasized by the Office within its published Examination Guidelines. *See Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International v. Teleflex Inc. Fed. Reg.* 72:57526-57535 (October 10, 2007), hereinafter "Examination Guidelines." To establish a *prima*

facie case of obviousness it is not sufficient to merely combine individual elements known in the prior art if the results would not have been predictable to one of ordinary skill in the art (*see* Examination Guidelines at page 57529). Establishment of a *prima facie* case of obviousness requires that the Examiner factually show that the references in combination teach all of the elements of the claims, as well as provide a reasoned articulation that the combination of elements would have been known to produce a predictable result.

Here, Sebbel and Kojima, alone or in combination, do not teach or suggest all of the elements of the presently pending claims. Thus, the Examiner's burden of establishing a *prima facie* case of obviousness has not been satisfied.

1. The Sebbel reference

Sebbel neither discloses nor suggests the use of virus-like particles (VLP) of an RNA-bacteriophage as an antigen array with ghrelin or ghrelin peptides as antigens or antigenic determinants attached by way of a non-peptide covalent bond as required by the presently pending claims.

a.) RNA bacteriophages for the formation of an antigen array are not disclosed in Sebbel

By the Examiner's own admission, "Sebbel does not specifically teach an RNA bacteriophage." Office Action at page 6. However, the Examiner has maintained the rejection alleging that "the cited references, in combination, teach the claim limitations such as the repetitive antigen array comprised of a Qβ bacteriophage and a ghrelin peptide." Office Action at page 5. This allegation is incorrect and, more importantly, has no basis in the evidence of record. There is great variety of bacteriophages found in

nature; however, there is nothing in Sebbel that discloses or suggests using one bacteriophage over another. As one of ordinary skill would be aware, bacteriophages not only differ in their various morphologic forms, they also differ in their genetic material in that they comprise either DNA or RNA. These forms are further divided into single- or double-stranded arrangements that are further divided into linear, circular or supercoiled arrangements. As admitted by the Examiner, Sebbel does not disclose RNA-bacteriophages. Indeed Sebbel only discusses bacteriophages in passing and does not provide specific disclosure or specific examples thereof.

To establish a *prima facie* case of obviousness involving structurally similar compounds, the Examiner must provide a showing that there is adequate support in the prior art for the changing the structure of a compound disclosed in the primary reference. *See Takeda Chem. Inds. v. Alphapharm*, 492 F.3d 1350, at 1356 (2007), citing *In re Grabiak*, 769 F.2d 729, at 731-732 (Fed. Cir. 1985). There is also the additional requirement that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention," *id.* citing *In re Jones*, 958 F.2d 347 (Fed. Cir.1992); *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985); *In re Lalu*, 747 F.2d 703 (Fed.Cir.1984). Thus, the holding in *Takeda* provides that a *prima facie* case of obviousness requires the identification of a lead compound (*e.g.*, a DNA or RNA bacteriophage) in the primary reference, followed by a clear articulation of the reasons why the artisan would change the compound (*e.g.*, a DNA or RNA bacteriophage) in a particular way to achieve a predictable result.

Sebbel discloses that the core particle could be, *inter alia*, a virus, a bacteriophage, or a virus-like particle, but Sebbel **does not disclose** that the core particle

could be (i) a RNA-bacteriophage or (ii) the RNA-bacteriophage Q-beta, or even that the core particle could be (iii) a virus-like particle of a bacteriophage or even (iv) a virus-like particle of an RNA-bacteriophage such as RNA-bacteriophage Qβ, as are recited in the presently pending claims and specifically defined in the present specification.

The description and example sections of Sebbel provide further evidence that Sebbel does not disclose core particles of RNA bacteriophage such as Qβ. In the example section of Sebbel, the core particles are made up of either (a) various HBcAgs, *i.e.,* specific virus-like particles derived from the Hepatitis B virus (*see* Sebbel, column 4, line 37; column 5, lines 38-52; and in particular column 20, line 36 to column 27, line 18) or (b) type-1 pili of *E.coli., i.e.* a specific bacterial pilus (*see* Sebbel, column 5, lines 53-67; and in particular column 27, line 19 to column 29, line 62). As a consequence, Sebbel **does not disclose** that the core particle could be (i) an RNA-bacteriophage such as the RNA-bacteriophage Q-beta, or (ii) a virus-like particle of a bacteriophage, or even (iii) a virus-like particle of an RNA-bacteriophage.

The presently pending claims are directed to core particles comprising a virus-like particle of an RNA-bacteriophage. Applicants respectfully assert that the Examiner has failed to identify an RNA-bacteriophage, such as a Qβ-phage, or as required in the present claims, a VLP of an RNA-bacteriophage, such as a VLP of Qβ-phage as a lead compound based on the teachings of Sebbel. As admitted by the Examiner, Sebbel does not teach an RNA-bacteriophage or Qβ-bacteriophage. Thus, Sebbel does not disclose all the elements of the presently pending claims.

b.) Virus-like particles of an RNA-bacteriophage are not disclosed in Sebbel

As indicated, the Examiner asserts that "Sebbel teaches a VLP bacteriophage coupled to an antigen by way of non-peptide bond." Office Action page 6. Furthermore, the Examiner asserts that "because Sebbel teaches the claim limitation such an ordered and repetitive antigen array with VLP bacteriophage by way of non-peptide bond it would have been obvious to the skilled person in the art to provide the composition of the present invention." Office action at page 6. Applicants respectfully disagree with the Examiner's assertions and the conclusion based thereon.

Contrary to the Examiner's assertion, the Sebbel reference **does not disclose** RNA-bacteriophages, VLPs of an RNA-bacteriophage, nor VLPs of an RNA-bacteriophage Qβ. The presently pending claims, and specifically independent claim 63, are drawn to compositions comprising VLP of an RNA-bacteriophage. Although, bacteriophages in general are mentioned in Sebbel, the reference does not disclose RNA bacteriophage as admitted by the Examiner (*see* Office Action at page 6), nor does it disclose a VLP of an RNA-bacteriophage, such as a VLP of Qβ-phage, as required in the present claims. To establish a *prima facie* case of obviousness, it is not enough to show that a claimed species or subgenus is encompassed by a prior art genus. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."). *See* also MPEP § 2144.08. Careful review of the paragraph in Sebbel relied on by the Examiner in support of her position reveals that there is no disclosure or suggestion in that paragraph of a Qβ phage or of an RNA bacteriophage in general, or, as required in the present claims, a VLP of an RNA-bacteriophage:

> In another embodiment, the core particle of the aforementioned composition comprises a virus, a virus-like particle, a bacterial pilus, a structure formed from bacterial pilin, a bacteriophage, a viral capsid particle or a recombinant form thereof. Alternatively, the core particle may be a synthetic polymer or a metal.

(Sebbel, column 5, lines 31-37.) Indeed, in the whole Sebbel document, there is **no disclosure** or suggestion of a Qβ-phage or an RNA-phage in general. Moreover, in the entire Sebbel document, there is **no disclosure** or suggestion of using a VLP of a Qβ-phage or a VLP of an RNA-phage in general to form an ordered and repetitive antigen array. As such, Applicants assert that the Sebbel reference is missing the element of a VLP of a Qβ-phage or VLP of an RNA-phage that is an element of the present claims.

c.) Knowledge gleaned from Applicants' disclosure cannot be used to formulate a rejection based on obviousness

The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). *See* also *KSR*, 127 S.Ct. 1727 at 1741 (quoting Federal Circuit statement with approval), and MPEP §2142. To sustain a rejection based on obviousness requires a showing that only knowledge which was within the level of ordinary skill at the time the claimed invention was made is used, and does not include knowledge gleaned only from the Applicant's disclosure. *See In re McLaughlin*, 443 F.2d 1392 (CCPA 1971), and MPEP §2142. Here, Applicants assert that the Examiner has impermissibly used the teaching of the present specification in an attempt to establish a *prima facie* case of obviousness. Specifically, the Examiner asserts:

> The present specification teaches: [0019] "(...), the highly repetitive and organized structure of the core particles and VLPs, respectively, mediates the display of the ghrelin or ghrelin-derived peptide in a highly ordered and repetitive fashion leading to a highly organized and repetitive antigen array." [0190] "(...) the use of the VLPs as carriers allow the formation of robust antigen arrays and conjugates, respectively, with variable antigen density. In particular, the use of VLPs of RNA phages, and hereby in particular the use of the VLP of RNA phage Qβ coat protein allows achievement of a very high epitope density.

Office Action at page 5. Thus, it is clear that in making this rejection, the Examiner has applied the teachings of the present specification to provide a rationale for the assertion that the references in combination produce a predictable result. However, this use of the present specification is not permissible to formulate a rejection based on obviousness. Applicants submit that the Examiner has failed to meet the burden for establishing a *prima facie* case of obviousness based on the teachings of Sebbel.

2.) The Kojima reference

The deficiencies of Sebbel are not cured by Kojima. This reference also does not disclose or suggest the use of an RNA bacteriophage such as Qβ, or as required in the present claims, the use of a VLP of an RNA-bacteriophage, such as a VLP of Qβ-phage as an antigen array for the attachment of ghrelin or ghrelin peptide through a non-peptide covalent bond. Kojima reports the purification and identification of ghrelin as an endogenous ligand specific for growth-hormone secretagogues receptor (GHS-R) (abstract of Kojima). Specifically, Kojima discloses the purification procedure, the determination of amino acid sequence of rat and human ghrelin, the characterization of the O-n-octanoylation of serine at position 3, the biochemical property of ghrelin as well as its expression pattern in various tissues.

In its method section, Kojima reported using ghrelin 13-28 coupled to KLH for the generation of polyclonal antibodies for the staining of ghrelin in neurons. As would be understood by one of ordinary skill, the generated antibodies were used as a research tool for the localization of ghrelin in the brain (Kojima, page 659, right column, lines 8-17). However, Kojima does not disclose the generation of immune responses against ghrelin for any other purpose.

In summary, there is no reason, suggestion, or motivation in Sebbel or in Kojima that would have led one of ordinary skill in the art to combine the references to arrive at the presently claimed invention. Even if there were reasons to combine the references, which there are not, the references in combination would be missing the essential element of a VLP of an RNA bacteriophage. Therefore, the Examiner has not met the burden of establishing a *prima facie* case of obviousness based on Sebbel in view of Kojima.

For at least these reasons, the presently claimed invention is not rendered obvious by Sebbel or Kojima, alone or combination. Applicants therefore respectfully request that the Examiner reconsider and withdraw the present rejection as it may apply to the presently pending claims 63, 68-76, 78-88, 94, 95 and 97-133 under 35 U.S.C. § 103(a).

II. Claims 4, 6-8, 11-14, 31, 63, 68-70, 72, 73, 75 and 85

The Examiner has maintained the rejection of claims 4, 6-8, 11-14, 31, 63, 68-70, 72, 73, 75 and 85 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sebbel *et al.* (U.S. Patent No. 6,964 769 B2, hereinafter "Sebbel") view of Kojima *et al.* (Nature, 1999, hereinafter " Kojima") and further in view of Vasiljeva *et al.* (FEBS Letters, 1998,

hereinafter "Vasiljeva") and Maita *et al.* (Gen Pept Accession # VCBPQB, 1971). Specifically, the Examiner asserts that:

> Vasiljeva was cited for the purpose of showing that antigen conjugated bacteriophages (generally taught by Sebbel) such as a specific RNA Qβ bacteriophage, have been known and used in the art at the time the present inveition was made. Maita complements Vasiljeva by disclosing the RNA Qβ bacteriophage which sequence is identical to the currently claimed SEQ ID NO; 4.

Office Action at page 7. Claims 4, 6-8, 11-14 and 31 have been canceled. Insofar as the rejection may apply to the remaining presently pending claims, Applicants respectfully traverse this rejection.

1.) The Sebbel and Kojima references

The deficiencies of Sebbel and Kojima have been discussed in detail above, and the reasons why these references cannot support an obviousness rejection set forth above are reiterated and incorporated herein by reference in their entirety.

2.) The Vasiljeva reference

Vasiljeva does not cure the deficiencies of Sebbel and Kojima; this reference does not disclose or suggest an RNA bacteriophage VLP, such as Oβ, in which the antigen is attached via a non-peptide covalent bond. Instead, Vasiljeva discloses the use of C-terminal UGA extension of the short form of a Qβ coat protein, a so-called A1 extension, as a target for presentation of foreign peptides on the outer surface of mosaic Qβ particles. However, only the 5 amino acid short preS1 epitope 31-DPAFR-35 of the hepatitis B surface antigen has been disclosed in Vasiljeva (*see* Vasiljeva, abstract). Here, the short foreign peptide is expressed as a fusion protein with A1. There is nothing in the reference that discloses or suggests attaching such a 5 amino acid short peptide to

the A1 extension or to the Qβ coat protein using a non-peptide bond. Finally, there is nothing in the reference that discloses or suggests attaching ghrelin or ghrelin peptides as antigens or antigenic determinants to form an ordered and repetitive antigen array.

Thus, at best Vasiljeva discloses the production of a fusion protein with an RNA-bacteriophage Qβ coat protein. The reference does not disclose using the VLP of Qβ phage for the production of a repetitive antigen array in which the antigens are attached via non-peptide covalent bond to the VLP of Qβ phage particles. Hence, this reference dos not cure the deficiencies of Sebbel and Kojima and cannot be combined therewith.

3.) The Maita reference

Maita also does not cure the deficiencies of Sebbel, Kojima and Vasiljeva; this reference does not disclose or suggest a RNA bacteriophage Qβ virus-like particle in which the antigen is attached via a non-peptide covalent bond. Maita only discloses the amino acid sequence of the coat protein of bacteriophage Qβ. The reference does not disclose the production of a VLP comprising an RNA-bacteriophage Qβ coat protein, nor the production of a repetitive antigen array in which the antigens are attached via non-peptide covalent bond to the VLP of Qβ phage particles. Maita also does not disclose where, if at all, an antigenic peptide could or should be attached to produce an ordered and repetitive antigen array.

In summary, for the same reasons elaborated above, which are reiterated and entirely incorporated herein by reference, Sebbel and Kojima would not have rendered the claims obvious under 35 U.S.C. § 103. The defects in these references cannot be remedied by Vasiljeva and Maita alone or combination, at least because the Examiner has not demonstrated a reason to predictably combine Vasiljeva and Maita alone or

combination with the other two references with a reasonable expectation of success. Moreover, the fact that a claimed species or subgenus may be encompassed by a known genus is not sufficient by itself to establish a *prima facie* case of obviousness. *See In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994); *see also* MPEP § 2144.08.

For at least these reasons, Applicants respectfully assert that claims 63, 68-76, 78-88, 94, 95 and 97-133 are not rendered obvious under 35 U.S.C. § 103(a) by Sebbel in view of Kojima and further in view of Vasiljeva and Maita. Applicants therefore respectfully request that the Examiner reconsider and withdraw this rejection.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Ulrike W. Jenks
Attorney for Applicants
Registration No. 59,044

Date: 4/25/08

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

773822_1.DOC